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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,493	07/12/2001	Francois Rousseau	00852	3950

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EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/25/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/787,493	Applicant(s) ROUSSEAU, FRANCOIS	
	Examiner Jeanine A Goldberg	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *10-12,14 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,13 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

07/22/01

DETAILED ACTION

1. This action is in response to the papers filed September 9, 2002. Currently, claims 1-18 are pending. Claims 10-12, 14, 18 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

1. Applicant's election without traverse of Group I in Paper No. 8 is acknowledged.

Claims 10-12, 14, 18 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

The requirement is still deemed proper and is therefore made FINAL.

Priority

2. This application is a National Stage of International Application No. PCT/C99/00852, filed September 15, 1999.

New Matter

2. Claims 8-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "non-cancerous cells" and "tissue" are included. The amendment was made in the international stage application. However, the specification does not describe or discuses "non-cancerous cells" and "tissue". Instead the specification describes merely a sample comprising the CAG repeat containing nucleit acid sequence (i.e. DNA, RNA, cDNA). This description does not support tissue or non-cancerous cells. The concept of "non-cancerous cells" and "tissue" does not appear to be part of the originally filed invention. Therefore, "non-cancerous cells" and "tissue" constitutes new matter. Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-9, 13, 15-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method for determining an individual's predisposition to breast cancer, development of breast cancer or responsiveness to therapy for breast

cancer by determining a polymorphism at the CAG repeat of the androgen receptor (AR) gene or **any** DNA variant equivalent or **any** mutation which shows a linkage disequilibrium therewith.

The specification asserts that the CAG mutation in AR is correlated with the an individuals predisposition to breast cancer, development of breast cancer or responsiveness to therapy for breast cancer.

There is not adequate description of the genus of **any** DNA variant equivalent or **any** mutation which shows a linkage disequilibrium therewith. The specification only discloses one variant within the scope of the genus: **any** DNA variant equivalent or **any** mutation which shows a linkage disequilibrium therewith. The specification only discusses the CAG repeat polymorphism as variants in the AR gene. The specification is silent with respect to mutations in linkage disequilibrium or DNA variant equivalents. The general knowledge in the art concerning variants in linkage disequilibrium with the CAG repeat polymorphism in AR does not provide any indication of how to readily identify these variants. The single variants described is not representative of the genus of AR variants. There is substantial variability among the species of nucleic acids encompassed in the scope of the claim because only one specific mutation has been identified in the gene and analyzed for association with breast cancer. The specification has also not defined a structural feature of the variants which would be common to all members of the genus that constitutes a substantial portion of the genus. Furthermore, one of skill in the art would conclude that applicant was not in possession of the claimed "**any** DNA variant equivalent or **any** mutation which shows a linkage disequilibrium

therewith" because the description of only two members of this genus is not representative of the variants of the genus and is insufficient to support the claims. Thus, the specification does not adequately provide a written description for **any** DNA variant equivalent or **any** mutation which shows a linkage disequilibrium therewith.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-9, 13, 15-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to methods of determining an individual's predisposition to breast cancer, development of breast cancer and/or responsiveness to therapy for breast cancer by determining a polymorphism at the CAG repeat of the androgen receptor (AR) gene or a DNA variant equivalent or a mutation which shows a linkage disequilibrium therewith.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman.

> They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The specification teaches analysis of 262 breast cancer patients and 465 control women for the CAG repeat coding for a polyglutamine tract in the 4' part of the AR gene located on chromosome X (page 29, lines 13-15). The specification teaches that "because of the large number of alleles identified (15 different alleles) the alleles were grouped arbitrarily in categories by size to simplify the analysis and increase the number of individuals in each category. The specification appears to group the alleles into five different groups A-E based upon the length, A alleles being the shortest, E alleles being the longest (page 29 of the specification). Additionally the specification appears to label various CAG genotypes with the designations XX or XY or XZ or YY or YZ or ZZ. None of these designations are informative to indicate what constitutes a short or long allele as required by the claims. The specification teaches that "the AR genotype was not associated with a significant risk of breast cancer in women with no history of breast benign disease (page 32, lines 30-32).

The art teaches, namely Ethaji et al. (Am. J. of Human Genetics, Vol. 61, No. 4, suppl 28.10.1997-1.11.1997, page A64), an association between the polymorphic CAG repeat of the androgen receptor and female breast cancer. Ethaji teaches that exon 1, which contains a polymorphic CAG repeat that modulates transactivation varies in length. The CAG repeat is normally in the rage of 11-33 repeats. Ethaji evaluates the association between the repeat length and the risk of breast cancer. Using PCR, 160

alleles were estimated and results indicated a significant shift to greater length in distribution of CAG repeat lengths in breast cancer samples. Ethaji also teaches that matching tumor and normal breast tissue.

Bharaj et al. (Clinical Biochemistry, Vol. 32, No. 5, pages 327-332, July 1999) teaches rapid and accurate determination of (CAG)n repeats in the androgen receptor gene using polymerase chain reaction and automated fragment analysis. Bharaj teaches that "we are now in the process of using this method for clinical studies involving prostate and breast cancer patients" (page 331, col. 2).

Moreover, the art teaches the unpredictability of the association. Spurdle et al. (J. of the National Cancer Institute, Vol. 91, No. 11, pages 961-966, June 2, 1999) teaches no evidence for an association between AR exon 1 CAGn length and breast cnacer risk in women under the age of 40 was found, despite having 80% power to detect modest effects (abstract). Spurdle amplified exon 1 polymorphic CAG repeat region in the Australian population but found no association between CAG lengths and breast cancer risk (Figure 1, Table 2, Table 3). Spurdle teaches that irrespective of how the CAGn greater than or equal to 22 allele status was modeled, there was no association with breast cancer, either before or after adjustment for the risk factors identified in the full dataset (page 964, col. 30).

Given et al. (Eur. J. of Cancer. Vol. 36, pages 533-534, March 2000) teaches that the AR CAG repeat appears not to be a modifier of age of onset in unselected breast cancers (page 534, col. 2). Given teaches that no effect of repeat length on age of presentation was found and there was no association between repeat length and

family history (abstract, page 534, col. 1). Given provides comments on the work of Rebbeck, stating that the influence of AR on breast cancer detected may (i) be restricted to women with the hereditary breast/ovarian cancer syndrome; (ii) results from linkage disequilibirum between AR repeat alleles and other variation nearby; or (iii) be a chance finding (page 534, col. 2). Given states that AR CAG repeat genotype is probably of little clinical importance for the general population.

Kadouri et al (Br. J. of Cancer, Vol. 85, No. 1, pages 36-40, July 2001) teaches that no association of the CAG repeats with breast cancer risk in either BRCA1/2 carrier or in the general population was found (abstract). Additionally, no significant association was found if restricted to the Ashkenazi carriers or only to BRCA1 or BRCA2 carriers (abstract). Kadouri suggests that if there is any effect of the AR repeat length on BRCA1 penetrance, it is likely to be weak. Kadouri attempted to replicate the observation of Rebbeck that found the longer repeat lengths, particularly genotypes with greater than 27 repeats, were associated with a higher risk of breast cancer. However, Kadouri's study based mainly on subjects from the Ashkenazi Jewish population failed to find any significant association of the AR repeat polymorphism with risk of breast cancer (page 40, col. 1). The same method of analysis was used, but no significant results were obtained. Kadouri teaches that since the distribution of CAG repeat length differed between populations and the distribution of disease status and age at onset also differed it was necessary to correct for population in the analysis by stratification.

Menin et al (Cancer Letters, Vol. 168, pages 31-36, July 2001) teaches that the AR CAG polymorphisms does not act as a modifier of tumor onset or tumor phenotype

in breast/ovarian cancer families (abstract). Additionally Haiman et al (Cancer Research, Vol. 62, pages 1045-1049, February 2002) teaches no overall relation for AR genotype with breast cancer risk among mostly postmenopausal Caucasian women was observed. Haiman summaries several studies among women from high-risk breast cancer families, and most but not all studies of sporadic breast cases do not support the association between AR CAGn repeat length and breast cancer risk (page 1045, col. 2).

Neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed. The specification and the claims of the instant application asserts that detection of CAG alleles within exon 1 of AR gene are indicative of breast cancer. The evidence for this assertion provided in the specification, in Table 1 and 2, pages 31-34, does not appear to support the broad scope of the assertion. First the specification has not provided an association between any DNA variant equivalent or a mutation which shows a linkage disequilibrium therewith. It is unpredictable that such mutations exist. Undue experimentation would be required to ascertain the identity of DNA variant equivalent or a mutation which shows a linkage disequilibrium therewith. While one could conduct additional experimentation to determine additional mutations which are "equivalents" or mutations which shows linkage disequilibirum, and the perform the association analysis to determine whether these newly identified variations might be associated with increased or decreased predisposition to breast cancer, the outcome of such research cannot be predicted and such further research and experimentation are both unpredictable and undue.

Furthermore, the teachings of the prior art do not provide evidence of how to use the methods in which CAG repeats are an indicator of breast cancer. The teachings of the specification do not establish that one could actually detect short, intermediate or large alleles as an indicator of breast cancer. As discussed above, there is not description or explanation of the range of CAG repeats and what constitutes a short, intermediate or long allele. Rather the teachings of the specification illustrate that A* +BB when compared to BC to EE genotypes is significant. There is not teachings or explanations what this analysis means. Furthermore, the analysis of three different levels, XYZ, does not provide whether there is any significant difference in p-values. The specification teaches that "the AR genotype was not associated with a significant risk of breast cancer in women with no history of breast benign disease (page 32, lines 30-32). Moreover, the closest art teaches that it is unpredictable as to whether one could successfully use the claimed invention. The post filing date art establishes that the association between CAG repeat lengths is not predictably associated with breast cancer risk among mostly post menopausal Caucasian women; in breast/ovarian cancer families; in BRCA1/2 carriers or general population; Ashkenazi carriers; or in early-onset breast cancer in the Australian population. Given the fact that neither the specification nor the art provide evidence of a correlation or association between certain ranges of alleles (short, intermediate and long) in breast cancer, it is further unpredictable as to whether any quantity of experimentation would allow one to practice the claimed invention. Accordingly, it would require undue experimentation for a skilled artisan to use the claimed invention.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-9, 13, 15-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-9, 13, 15-17 are indefinite over the recitation "a DNA variant equivalent" because it is unclear what is encompassed by a DNA variant equivalent. Each DNA variant differs in structure and many differ in function. Therefore, it is unclear what constitutes an equivalent DNA variant. It is unclear whether equivalence is determined by equivalent structure, equivalent function or some other means of equivalence.

B) Claims 1-9, 13, 15-17 are indefinite because the claim does not particularly set forth how to achieve the preamble requirements. The claim merely recites that the determining of a polymorphism enables a prediction of an individual's predisposition to breast cancer, development of breast cancer and/or responsiveness to therapy for breast cancer, however, the claim does not set forth how such is accomplished. It is unclear whether the detection of a polymorphism is associated with an increase or decrease in predisposition to breast cancer. It is unclear whether all polymorphisms have the same function of affection the predisposition in the same manner.

C) Claims 2-5, 15 are indefinite over the recitation "the androgen receptor genotype" because the recitation lacks proper antecedent basis. Claim 1 requires determining a polymorphism, but the claim does not recite determining a genotype. Therefore, proper antecedent basis is lacking. This rejection may be easily overcome by amending Claim 1 to recite "determining the androgen receptor genotype by detecting a CAG repeat polymorphism in exon 1."

D) Claims 4-5 are indefinite over the recitation "derived from a nucleic acid sequence" because this language does not particularly set forth whether the pair of primers are limited to fragments of the androgen receptor gene or can include sequences which were originally taken from the androgen receptor gene but are then modified in sequence, i.e. by additions, deletions, substitutions, such that the probe sequences are not the same as given in the androgen receptor gene.

E) Claims 13, 15-17 are indefinite over the recitation "the shortest alleles," "intermediate to large alleles" because the description of the alleles are relative terms. The term "the shortest alleles," "intermediate to large alleles" in claims 13, 15-17 are relative terms which renders the claim indefinite. The terms "the shortest alleles," "intermediate to large alleles" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification is silent with respect to the number of CAG repeats which constitute short, intermediate or larger alleles. There is not indication in the specification what range of alleles are encompassed by these relative terms. The specification appears to group the alleles

into five different groups A-E based upon the length, A alleles being the shortest, E alleles being the longest (page 29 of the specification). Additionally the specification appears to label various CAG genotypes with the designations XX or XY or XZ or YY or YZ or ZZ. None of these designations are informative to indicate what constitutes a short or long allele as required by the claims. Therefore, the metes and bounds of the claimed invention are unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-4, 6-9, 13, 15-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Rebbeck et al. (Am. J. Hum. Genet. Vol. 64, pages 1371-1377, April 1999).

It is noted that the claims as written are methods which do not require any specific result to be obtained. The only positive process step is determining a polymorphism at the CAG repeat of AR gene.

Rebbeck teaches analyzing AR alleles for CAG repeat length polymorphism found in exon 1 of the AR gene. Alleles containing longer CAG repeat lengths are associated with a decreased ability to activate androgen-responsive genes. Rebbeck

teaches that women were at significantly increased risk of breast cancer if they carried at least one AR allele with greater than 27 CAG repeats (abstract). Rebbeck samples genomic DNA from peripheral blood and PCR amplified the CAG trinucleotide repeat. Statistical analysis was performed using Cox proportional hazards models. Figure 1 illustrates the distribution of cancer-free women and breast cancer cases and AR CAG repeats. Rebbeck teaches that a skew in the distribution of breast cancer cases was seen (page 1373, col. 2). Moreover, Rebbeck teaches that female BRCA1 mutation carriers who have inherited at least one very long AR-CAG repeat may be diagnosed with breast cancer at significantly earlier age than women who do not carry a very long AR-CAG repeat (page 1376, col. 1).

8. Claims 1-4, 6-9, 13, 15-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Ethaji et al. (Am. J. of Human Genetics, Vol. 61, No. 4, suppl 28.10.1997-1.11.1997, page A64).

It is noted that the claims as written are methods which do not require any specific result to be obtained. The only positive process step is determining a polymorphism at the CAG repeat of AR gene.

Ethaji et al. (herein referred to as Ethaji) teaches an association between the polymorphic CAG repeat of the androgen receptor and female breast cancer. Ethaji teaches that exon 1, which contains a polymorphic CAG repeat that modulates transactivation varies in length. The CAG repeat is normally in the rage of 11-33 repeats. Ethaji evaluates the association between the repeat length and the risk of

breast cancer. Using PCR, 160 alleles were estimated and results indicated a significant shift to greater length in distribution of CAG repeat lengths in breast cancer samples. Ethaji also teaches that matching tumor and normal breast tissue.

9. Claims 1-9, 13, 15-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Bharaj et al. (Clinical Biochemistry, Vol. 32, No. 5, pages 327-332, July 1999).

It is noted that the claims as written are methods which do not require any specific result to be obtained. The only positive process step is determining a polymorphism at the CAG repeat of AR gene.

Bharaj et al. (herein referred to as Baraj) teaches rapid and accurate determination of (CAG)n repeats in the androgen receptor gene using polymerase chain reaction and automated fragment analysis. Bharaj teaches that "we are now in the process of using this method for clinical studies involving prostate and breast cancer patients" (page 331, col. 2)(limitations of Claim 1-2). Bharaj teaches a method of extracting DNA from whole blood and subjecting the nucleic acid to PCR amplification (limitations of Claim 3-4, 6-7, 9). Bharaj also teaches the possibility of amplifying genomic DNA from serum. Bharaj teaches a paired primer set which corresponds to SEQ ID NO: 1 and 2 of the instant application (limitations of Claim 5). Bharaj illustrates the distribution and allele frequency of CAG repeats in females (page 331, Figure 4).

Conclusion

10. No claims allowable.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
November 20, 2002

W. Gary Jones
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